Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting Information for: Regulation of oligonucleotide adsorption by a thermo and pH dual-responsive copolymer layer

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1. Supplementary method

1.1. Numerical methodology

Here we present an outline of the numerical method used to solve the equations derived from the molecular theory. This is done by dividing the z-axis into parallel layers of thickness δ. Functions are assumed to be constant within a layer; hence integrations can be replaced by summations. The ith layer is defined as the region between $(i-1)\delta \leq z < i\delta$. The packing constraints, eq 11, in a discrete form for layer i is:

$$\sum_j \rho_j(i)v_j + \langle\phi_n(i)\rangle + \langle\phi_{ONs}(i)\rangle + \langle\phi_e(i)\rangle = 1. \tag{S1}$$

The volume fractions of PNIPAm and PEI equal

$$\langle\phi_j(i)\rangle = \sigma \sum_\alpha p(\alpha) n_j(\alpha, i) v_j. \tag{S2}$$

The volume fractions of oligonucleotide is

$$\phi_{ONs}(i) = \sum_{i'=1}^{i'=i'_{max}} \rho_{ONs}(i') \sum_{\beta_{i'}} p(\beta_{i'}) n_{ONs}(\beta_{i'}, i) v_{ONs}. \tag{S3}$$

Here the discretized probability distribution functions $p(\alpha)$ and $p(\beta_i)$ are

$$\begin{aligned} p(\alpha) \;=\; & \frac{1}{q_\alpha} \prod_{i=1}^{i=i_{max}} \exp\{-n_e(\alpha,i)[\ln(1-f(i)) + \beta\mu^0_{PEI}] \\ & -\frac{\chi_{nw}(i)}{v_w} n_n(\alpha,i) v_n \phi_w(i) - \frac{\partial\chi_{nw}(i)}{\partial\phi_n(i)} n_n(\alpha,i) v_n/v_w \phi_n(i)\phi_w(i) \\ & -\beta\pi(i)[n_n(\alpha,i)v_n + n_e(\alpha,i)v_e]\}, \end{aligned} \tag{S4}$$

and

$$p(\beta_i) \;=\; \frac{1}{q_{\beta_i}} \prod_{i=1}^{i=i_{max}} \exp\{-\beta\psi(i') n_{ONs}(\beta_i, i') q_{ONs} - \beta\pi(i') n_{ONs}(\beta_i, i') v_{ONs}\}. \tag{S5}$$

The volume fractions of cations, anions, protons, hydroxyl ions and water molecules are given by:

$$\phi_{Na^+}(i) = \phi^{bulk}_{Na^+} \exp[-\beta\psi(i)e - \beta(\pi(i) - \pi^{bulk})v_{Na^+}], \tag{S6}$$

$$\phi_{Cl^-}(i) = \phi^{bulk}_{Cl^-} \exp[\beta\psi(i)e - \beta(\pi(i) - \pi^{bulk})v_{Cl^-}], \tag{S7}$$

$$\phi_{H^+}(i) = \phi_{H^+}^{bulk} \exp[-\beta\psi(i)e - \beta(\pi(i) - \pi^{bulk})v_{H^+}], \tag{S8}$$

$$\phi_{OH^-}(i) = \phi_{OH^-}^{bulk} \exp[\beta\psi(i)e - \beta(\pi(i) - \pi^{bulk})v_{OH^-}], \tag{S9}$$

$$\phi_w(i) = \exp[-\beta\pi(i)v_w - \chi_{nw}(i)\langle\phi_n(i)\rangle]. \tag{S10}$$

The generalized Poisson equation is described as follows:

$$\epsilon[\frac{\psi(i+1) - 2\psi(i) + \psi(i-1)}{\delta^2}] = -\langle\rho_q(i)\rangle. \tag{S11}$$

$\langle\rho_q(i)\rangle$ is the total charge density in layer i, which is

$$\langle\rho_q(i)\rangle \ = \ \sum_j \rho_j(i)q_j + f(i)\langle\rho_e(i)\rangle e + \langle q_{ONs}(i)\rangle, \tag{S12}$$

and

$$\langle\rho_{ONs}(i)\rangle = \sum_{i'=1}^{i'=i'_{max}} \rho_{ONs}(i') \sum_{\beta_{i'}} p(\beta_{i'}) n_{ONs}(\beta_{i'}, i). \tag{S13}$$

The discrete boundary conditions are

$$\psi(1) - \psi(0) = 0, \tag{S14}$$

and

$$\psi(n+1) = 0. \tag{S15}$$

The discretized packing constraint and Poisson equation constitute a set of coupled nonlinear equations for $\pi(i)$ and $\psi(i)$. These coupled equations can be solved with standard numerical techniques.

1.2. Chain model

The chain model for PEI-b-PNIPAm is the three-state RIS model.[1] In this model, each bond has three different isoenergetic states. The copolymer conformations are generated by a simple sampling method and all the accepted conformations are self-avoiding. We generate 10^6 independent conformations. In our calculations, each segment of PNIPAm has the volume of v_n=0.16 nm^3, which was chosen according to the partial specific volume of PNIPAm in water. Each segment of PEI has the volume of v_n=0.085 nm^3, and for water

v_w=0.03 nm^3.[2] The layer thickness was δ=0.5 nm. The interaction parameter $\chi_{wn}(i) = (g_{00} + g_{02}T) + (g_{10} + g_{12}T)\phi_n(i) + (g_{20} + g_{22}T)\phi_n^2(i)$ between water and PNIPAm comes from the experiment of Afroze et al.[3]

The three-state RIS model is also used to generate conformations of oligonucleotide. 2×10^4 independent conformations are generated with the first segment at the first layer, and then they are transferred to each layer. In our calculations, z-axis is divided into n=50 layers. Namely, 10^6 conformations are generated for oligonucleotide. The length and the volume of oligonucleotide base are chosen as $l_{ONs} = 0.4nm$ and $v_{ONS} = 0.4nm^3$, respectively.[4] The same set of conformations has been used in all calculations presented in this paper.

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[1] C.-l. Ren and Y.-q. Ma, *Soft Matter*, 2011, **7**, 10841–10849.

[2] P. Kujawa and F. M. Winnik, *Macromolecules*, 2001, **34**, 4130–4135.

[3] F. Afroze, E. Nies and H. Berghmans, *J. Mol. Struct.*, 2000, **554**, 55–68.

[4] C.-l. Ren, R. Schlapak, R. Hager, I. Szleifer and S. Howorka, *Langmuir*, 2015, **31**, 11491–11501.

2. Supplementary figures

2.1. Planar surface

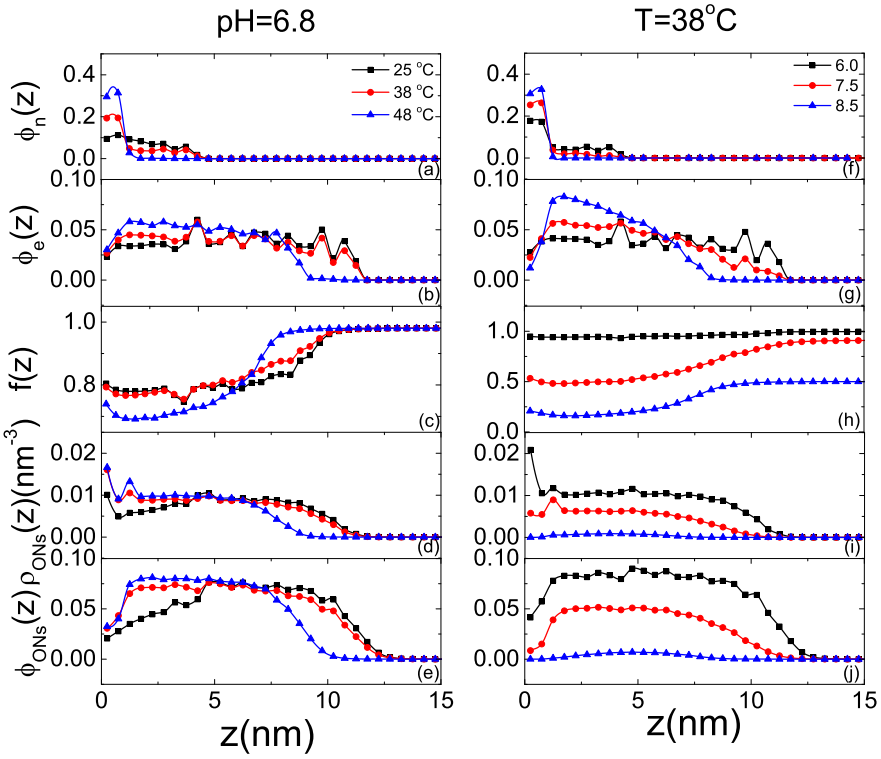

Fig. S1: (a-e) The molecular structures of the temperature-sensitive oligonucleotide adsorption at pH6.8, when temperature is 25 ^{o}C, 38 ^{o}C and 48 ^{o}C, respectively. The volume fraction of (a) PNIPAm and (b) PEI, (c) the degree of protonation, (d) the density and (e) volume fraction of adsorbed oligonucleotides as a function of distance from the substrate. (f-j) The molecular structures of the pH-sensitive oligonucleotide adsorption at 38 ^{o}C, when pH is 6.0, 7.5 and 8.5, respectively. The volume fraction of (f) PNIPAm and (g) PEI, (h) the degree of protonation, (i) the density and (j) volume fraction of adsorbed oligonucleotides as a function of distance from the substrate. Other parameters are the same as Figure 2a and b, respectively.

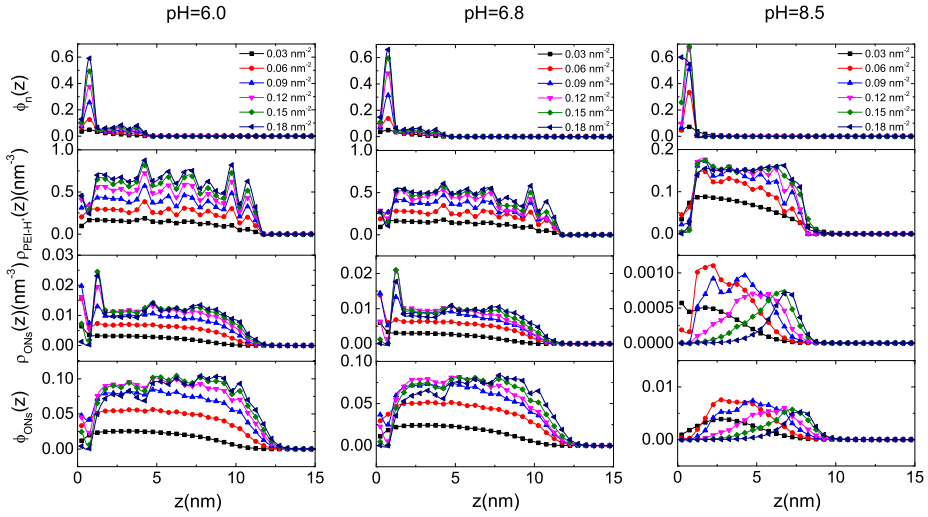

Fig. S2: The effect of copolymer surface coverage on the molecular distribution, when the pH is 6.0, 6.8 and 8.5 at 38 ^{o}C in the pH-responsive behavior of oligonucleotide loading. Other parameters are the same as Fig. 3.

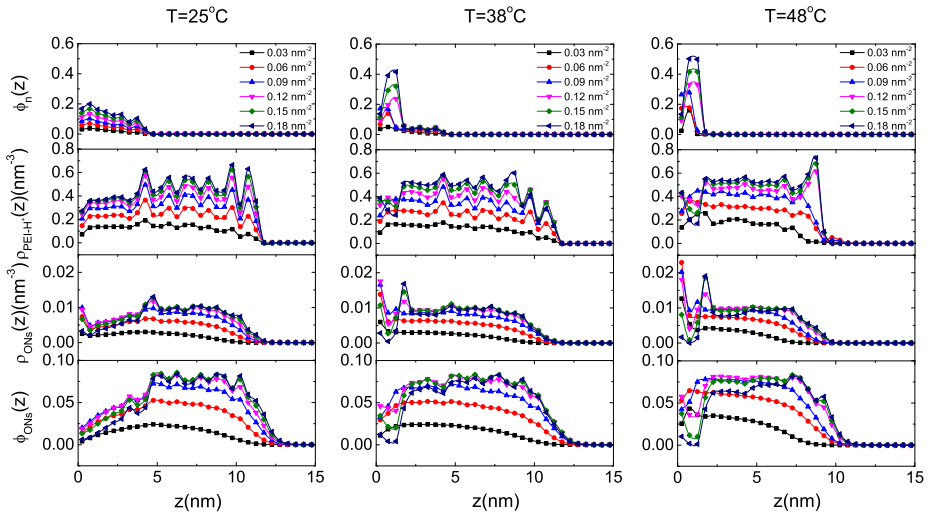

Fig. S3: The effect of copolymer surface coverage on the molecular distribution, when the temperature is 25 ^{o}C, 38 ^{o}C and 48 ^{o}C at pH6.8 in the thermo-responsive behavior of oligonucleotide loading. Other parameters are the same as Fig. 2.

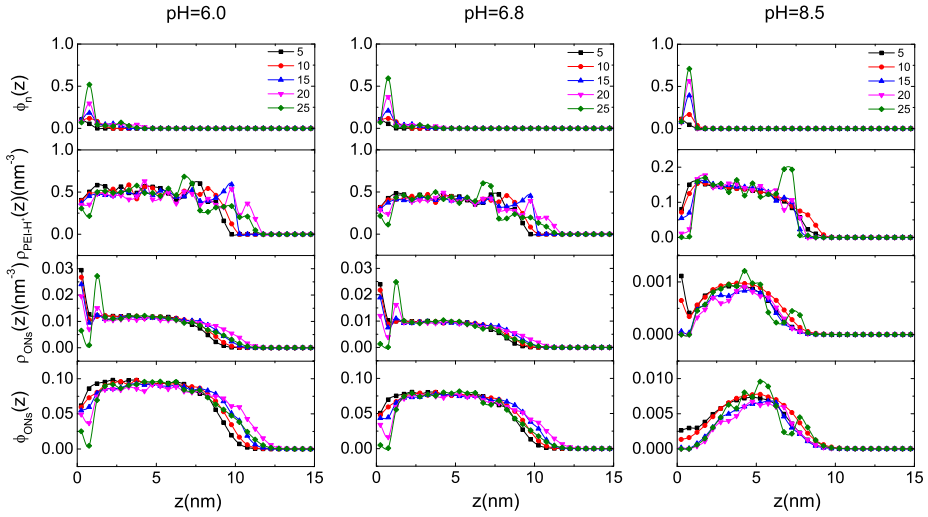

Fig. S4: The effect of PNIPAm length on the molecular distribution, when the pH is 6.0, 6.8 and 8.5 at 38 ^{o}C in the pH-responsive behavior of oligonucleotide loading. Other parameters are the same as Fig. 3.

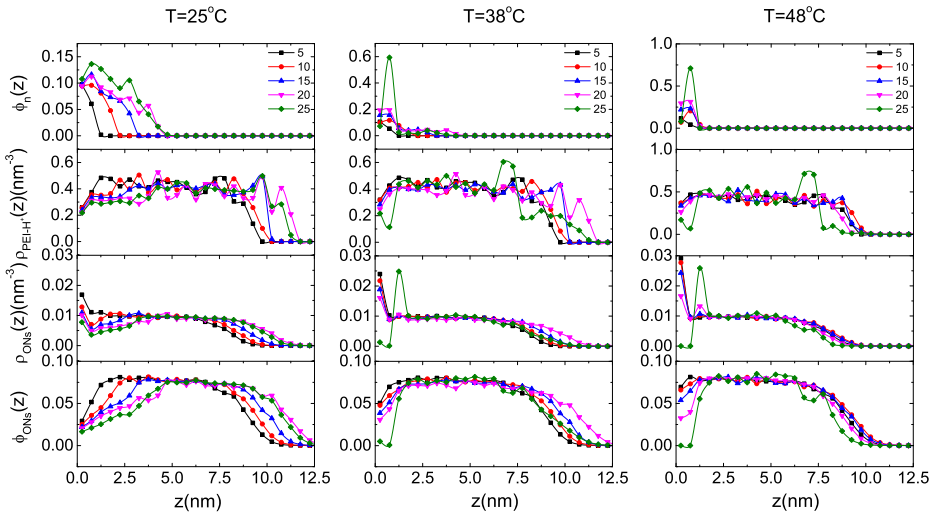

Fig. S5: The effect of PNIPAm length on the molecular distribution, when the temperature is 25 ^{o}C, 38 ^{o}C and 48 ^{o}C at pH6.8 in the thermo-responsive behavior of oligonucleotide loading. Other parameters are the same as Fig. 2.

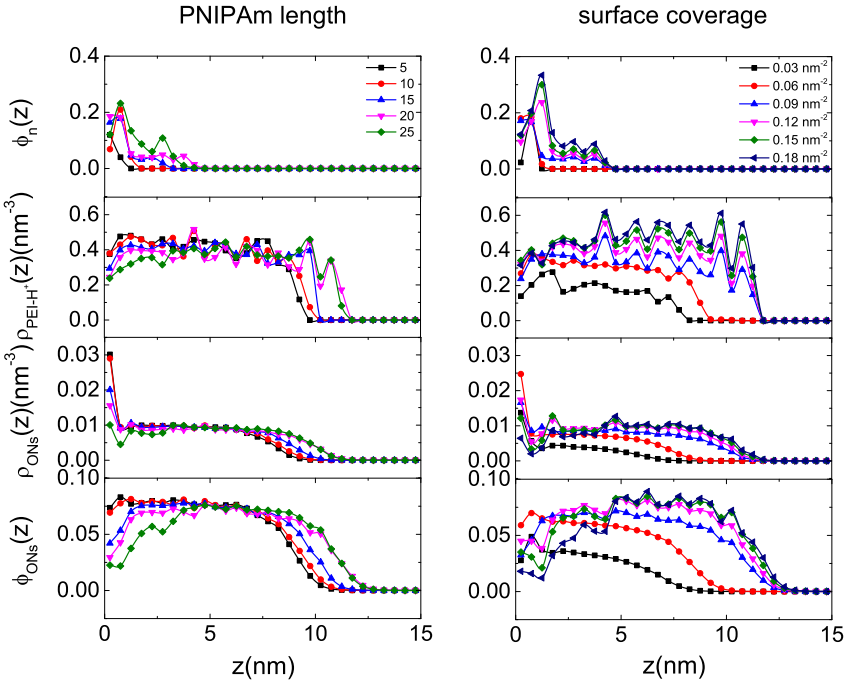

Fig. S6: The effect of PNIPAm length and surface coverage on the molecular distribution of the maximal loading capacity in the thermo-responsive behavior of oligonucleotide loading. Other parameters are the same as Fig. 2 and 3, respectively.

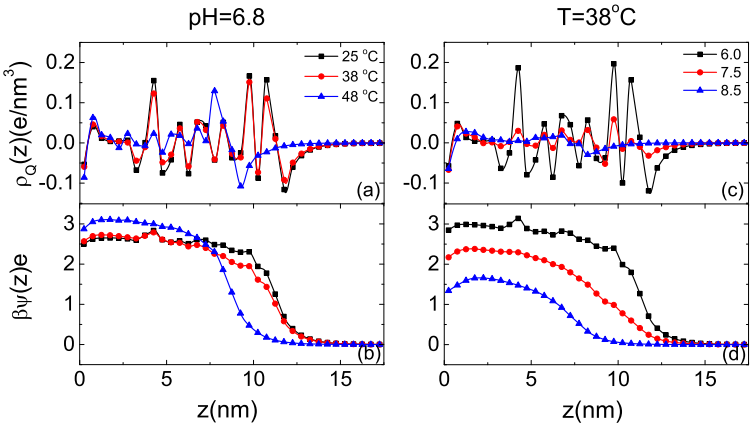

Fig. S7: (a) The average charge density and (b) electrostatic potential of the temperature-sensitive oligonucleotide adsorption as a function of the distance from the surface at pH6.8, when temperature is 25 ^{o}C, 38 ^{o}C and 48 ^{o}C, respectively. (c) The average charge density and (d) electrostatic potential of the pH-sensitive oligonucleotide adsorption as a function of the distance from the surface at 38 ^{o}C, when pH is 6.0, 7.5 and 8.5, respectively. Other parameters are the same as Figure 2a and b.

2.2. Nanoparticle

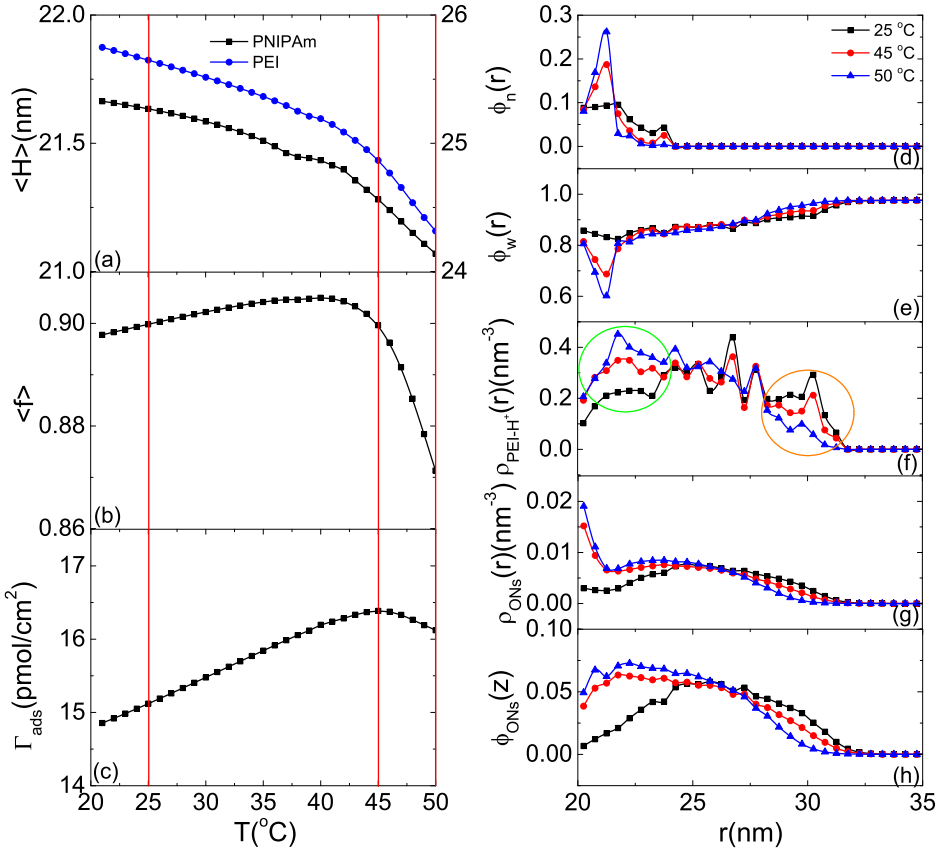

Fig. S8: (a-c) The thermo-responsive behavior of oligonucleotide adsorption. (a) The average height of PNIPAm and PEI, (b) the average degree of PEI protonation and (c) the number of adsorbed oligonucleotides as a function of temperature at pH6.8. (d-h) The molecular structures of the temperature-sensitive oligonucleotide adsorption at 25 ^{o}C, 45 ^{o}C and 50 ^{o}C, respectively, which are marked by vertical red lines in Fig. S5a-c. (d) The volume fraction of PNIPAm and (e) water, (f) the density of protonated PEI monomers, (g) the density and (h) volume fraction of adsorbed oligonucleotides as a function of distance from the substrate. Other parameters are the same as Fig. 2.

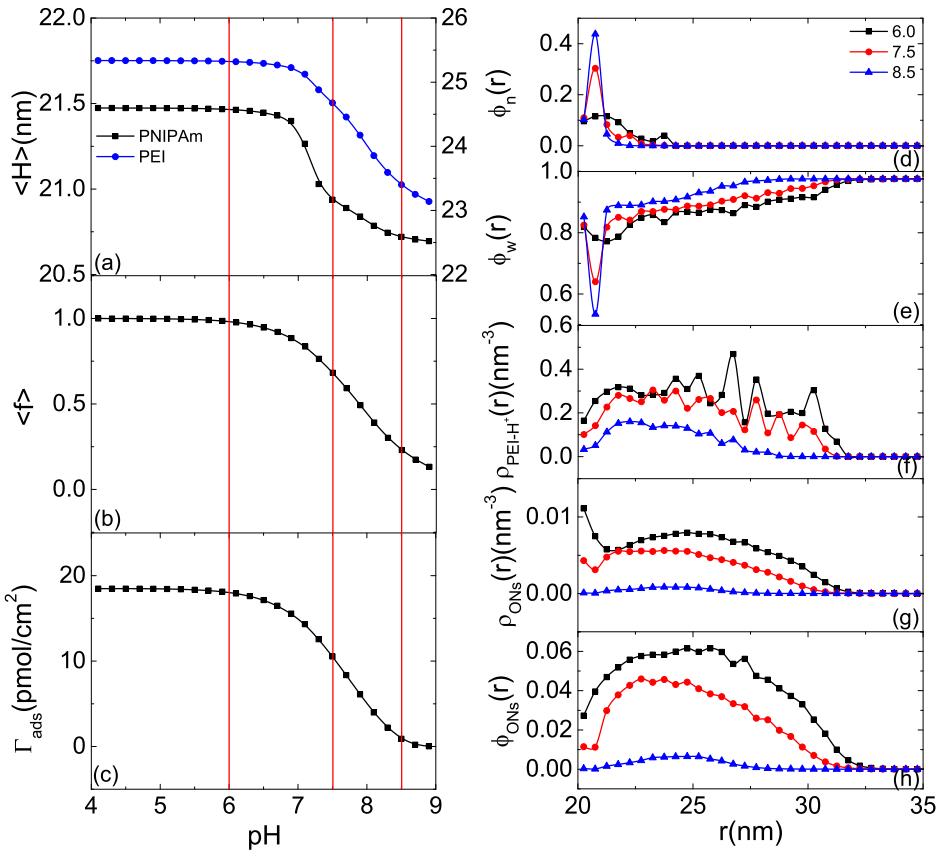

Fig. S9: (a-c) The pH-responsive behavior of oligonucleotide adsorption. (a) The average height of PNIPAm and PEI, (b) the average degree of PEI protonation and (c) the number of adsorbed oligonucleotides as a function of pH at 38 ^{o}C. (d-h) The molecular structures of the pH-sensitive oligonucleotide adsorption at 6.0, 7.5 and 8.5, respectively, which are marked by vertical red lines in Fig. S6a-c. (d) The volume fraction of PNIPAm and (e) water, (f) the density of protonated PEI monomers, (g) the density and (h) volume fraction of adsorbed oligonucleotides as a function of distance from the substrate. Other parameters are the same as Fig. 3.

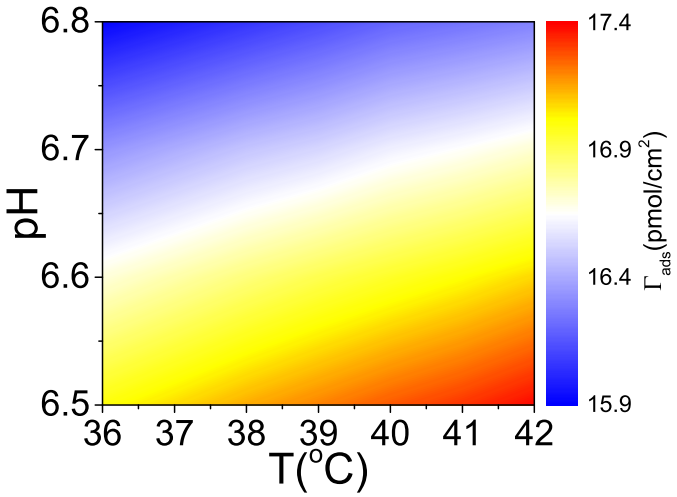

Fig. S10: The amount of adsorbed oligonucleotides as a function of temperature in vivo environment of malignant solid tumors (at pH6.5-6.8). Other parameters are the same as Fig. 2.

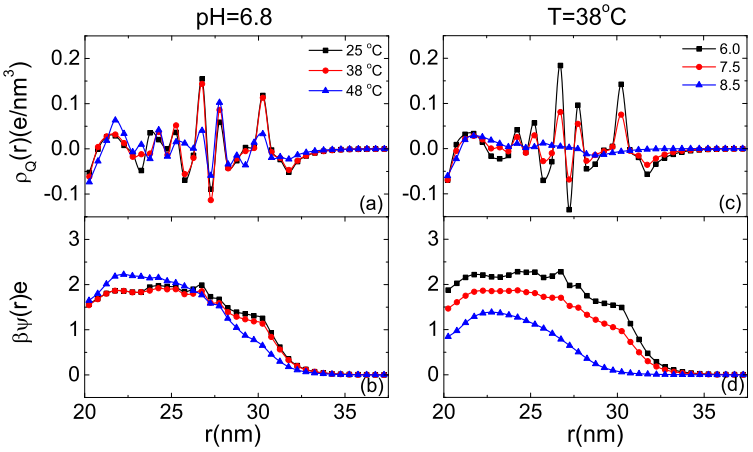

Fig. S11: (a) The average charge density and (b) electrostatic potential of the temperature-sensitive oligonucleotide adsorption as a function of the distance from the surface at pH6.8, when temperature is 25 ^{o}C, 38 ^{o}C and 48 ^{o}C, respectively. (c) The average charge density and (d) electrostatic potential of the pH-sensitive oligonucleotide adsorption as a function of the distance from the center of nanoparticle at 38 ^{o}C, when pH is 6.0, 7.5 and 8.5, respectively. Other parameters are the same as Figure 2a and b.

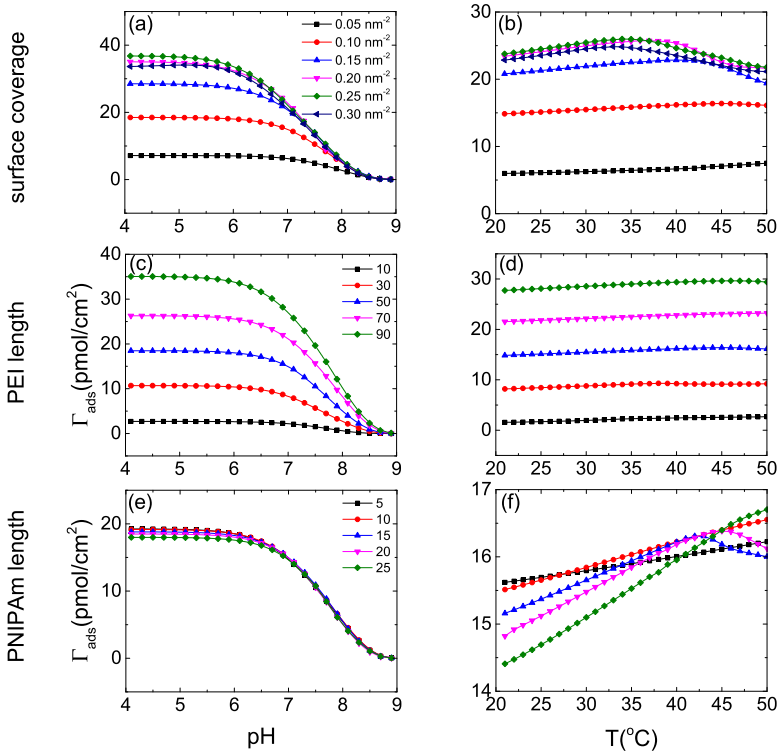

Fig. S12: The effect of (a and b) copolymer surface coverage, (c and d) PEI length and (e and f) PNIPAm length on the pH and thermo dual-responsive behaviors. Other parameters are the same as Fig. 2 and 3, respectively.

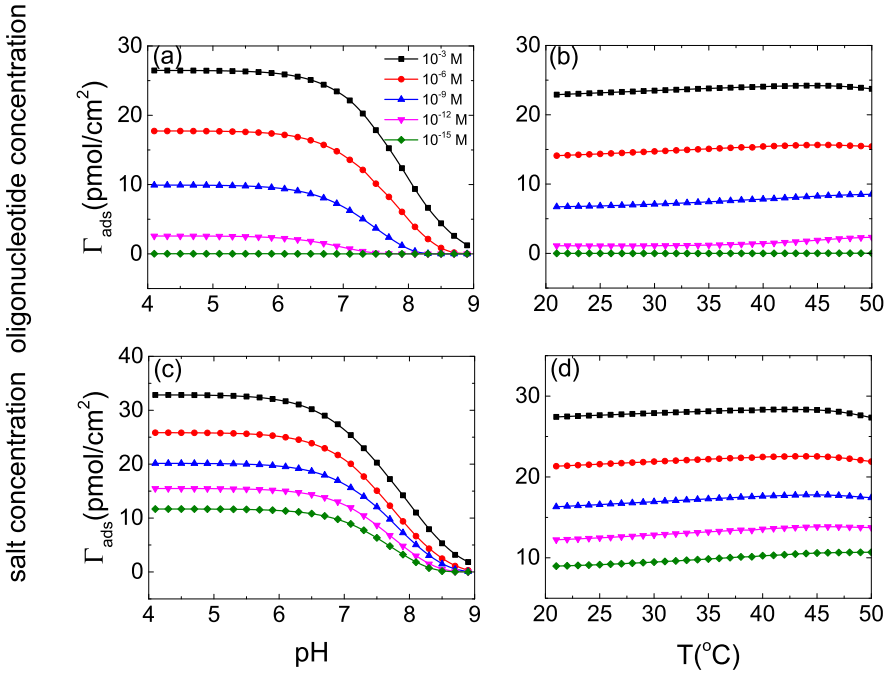

Fig. S13: The effect of (a and b) oligonucleotide concentration and (c and d) salt concentration in bulk solution on the pH and thermo dual-responsive behaviors. Other parameters are the same as Fig. 2 and 3, respectively.